

## Recommended comparator products: anti-tuberculosis medicines

Comparator products should be purchased from a well regulated market with stringent regulatory authority *i.e.*, from countries participating in the International Conference on Harmonization (ICH)<sup>1</sup>.

Invited medicinal products	Recommended comparator product (Strength, Manufacturer)
<i>Single ingredient first-line anti-tuberculosis medicines</i>	
Ethambutol, 100 mg and 400 mg tablet	Myambutol (400 mg tablet, Riemser Arzneimittel or Teopharma)
Isoniazid, 50 mg, 100 mg and 300 mg tablet	Isozid (100 mg tablet, Fatol) Isoniazid (100 mg, 300 mg tablet, Sandoz, US <sup>2</sup> )
Pyrazinamide, 150 mg and 400 mg tablet	Pyrazinamide Lederle (500 mg tablet, Riemser Arzneimittel)
Rifampicin, 150 mg and 300 mg capsule	Rimactane (150 mg tablet, Novartis or Sandoz) Rifadin (300mg capsule, Sanofi-Aventis, US <sup>2</sup> )
Streptomycin, 1 g powder for solution for injection (vial)	Streptomycin (1g/2.5ml injection, Pfizer, US <sup>2</sup> )
<i>Fixed-dose combination products of first-line anti-tuberculosis medicines:</i>	
Rifampicin 150 mg + Isoniazid 75 mg tablet	Rifinah (rifampicin 300 mg + isoniazid 150 mg tablet, Sanofi-Aventis), Rifamate (rifampicin 300 mg + isoniazid 150 mg capsule, Sanofi-Aventis, US <sup>2</sup> )
Rifampicin 60 mg + Isoniazid 30 mg + Pyrazinamide 150 mg tablet	Rifater (rifampicin 120 mg + isoniazid 50 mg + pyrazinamide 300 mg tablet, Sanofi-Aventis, US <sup>2</sup> )
For other invited fixed-dose combination products of anti-tuberculosis medicines, use appropriate combination of the recommended single ingredient comparator products	

<i>Single ingredient second-line anti-tuberculosis medicines</i>	
Amikacin, 250 mg/ml injection solution (vial 2ml), 1 g powder for solution for injection (vial)	Amukin or Amikin (250 mg/ml, injection solution; Bristol-Myers Squibb or Apothecon)
Capreomycin, 1 g powder for solution for injection (vial)	Capastat (1 g powder for solution for injection, Lilly)

<sup>1</sup> Countries officially participating in ICH are the ICH members European Union, Japan and USA; and the ICH observers Canada and EFTA as represented by Switzerland. Other countries associated with ICH (through legally binding mutual recognition agreements) include Australia, Norway, Iceland and Liechtenstein.

Cycloserine, 250 mg capsule	Seromycin (250 mg capsule, Lilly)
Ethionamide, 250 mg tablet	Trecator (250 mg tablet, Wyeth)
Kanamycin, 500 mg and 1g powder for solution for injection (vial)	Kantrex (1 g/3 ml, injection solution, Bristol-Myers Squibb or Apothecon)
Levofloxacin, 250 mg, 500 mg and 750 mg tablet	Tavanic (250 mg and 500 mg tablet, Sanofi-Aventis) Levaquin (750 mg tablet, Ortho-McNeil Janssen, US <sup>2</sup> )
Moxifloxacin, 400 mg tablet	Avelox (400 mg film-coated tablet, Bayer)
Ofloxacin, 200 mg and 400 mg tablet	Tarivid (200 mg tablet, Aventis Pharma) Ofloxacin (400 mg tablet, TEVA, US <sup>2</sup> )
Prothionamide, 250 mg tablet	Peteha (250 mg tablet, Fatol)
Terizidone, 300 mg capsule, tablet	Terizidex (250 mg capsule, Collect, Brazil) <sup>3</sup>

<sup>2</sup> The recommended comparator products are approved by US FDA; the comparator product should be obtained from the US market.

<sup>3</sup> Product should be purchased from the market of Brazil.

### **Obtaining Comparator**

Comparator products should be purchased from a well regulated market with stringent regulatory authority *i.e.*, from countries participating in the International Conference on Harmonization (ICH). If the recommended comparator cannot be located for purchase from the market of an ICH-associated country, the applicant should consult with WHO regarding the sourcing of an acceptable comparator product.

### **Information Requirements**

Within the submitted dossier, the country of origin of the comparator product should be reported together with lot number and expiry date, as well as results of pharmaceutical analysis to prove pharmaceutical equivalence. Further, in order to prove the origin of the comparator product the applicant must present all of the following documents:

1. Copy of the comparator product labelling. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.
2. Copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.
3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.
4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market. The certification should be signed by the company executive or equivalent responsible for the application to the Prequalification Programme.

### **Dose Equivalence**

In case the invited product has a different dose compared to the available acceptable comparator product, it is not always necessary to carry out a bioequivalence study at the same dose level; if the active substance shows linear pharmacokinetics, extrapolation between similar doses may be applied by dose normalisation.

### **Fixed-dose Combination Products**

The bioequivalence of fixed-dose combination (FDC) product should be established following the same general principles. The submitted FDC product should be compared with the respective innovator FDC product as listed above. In cases where a FDC comparator product is not listed above, individual component products administered in loose combination should be used as a comparator. The principles of dose normalization as mentioned above are applicable.

### **Suitability of a comparator product for BCS-based biowaiver applications**

Recommendation of an API for BCS-based biowaivers is made purely on the solubility, permeability, safety and related properties of the API (Class 1 or Class 3) – see the Biowaiver guidance documents on the WHO Prequalification website. It does not imply that the recommended comparator product(s) will be rapidly dissolving in case of Class 1 APIs (or very rapidly dissolving in case of Class 3 API), which is a requirement for BCS based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the Prequalification website is indeed suitable for a BCS based-biowaiver application before product development.

Note that rapidly dissolving (or very rapidly dissolving) properties of a product are not required for *in vivo* bioequivalence studies. Thus, though a listed comparator product may not be suitable for BCS-based biowaiver purposes, it is still suitable for *in vivo* bioequivalence studies.